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Practitioner's Docket No. U 014778-9

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Manne Satyanarayana **Reddy**, et al.

Serial No.: 10/647,449

Group No.: 1614

Filed: August 25, 2003

Examiner:

For: POLYMORPHIC FORMS OF (S)-REPAGLINIDE AND THE PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents

P. O. Box 1450

Alexandria, VA 22313-1450

TRANSMITTAL OF CERTIFIED COPIES

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country: INDIA

Application Number: 621/MAS/2002

Filing Date: August 23, 2002

Country: INDIA

Application Number: 637/MAS/2002

Filing Date: August 30, 2002

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(Transmittal of Certified Copies—page 1 of 2) 5-5



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NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification, Abstract & Drawings of the extract of Patent Application No.621/MAS/2002, dated 23.08.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

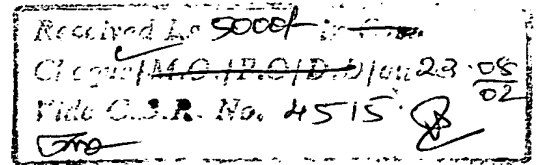
.....In witness thereof

I have hereunto set my hand

Dated this the 6th day of November 2003
15th day of Kartika, 1925(Saka)

(K.M. VISWANATHAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018



FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7 and Rule 33A)

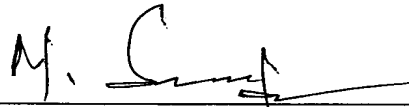
We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "**An Improved process for the preparation of crystalline Form-II of (S)-Repaglinide**".
- (b) that the complete specification relating to this invention is filed with this application.
- (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are **Manne Satyanarayana Reddy, Sajja Eswaraiah, Mathad Vijayavithal Thippannachar, Govindan Shanmugam, Maddipatla Madhavi and Kolla Naveen Kumar**. All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh**.
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

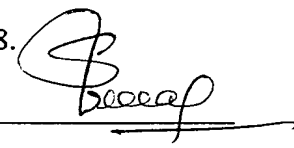
Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016

5. following declaration was given by inventors.
We, the true and first inventors for this invention declare that the applicant Herein is our assignee.

Signed)



Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
Kalyan Nagar,
Near AG Colony,
Erragadda,
Hyderabad-500 038.

Signed)

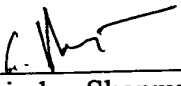

Sajja Eswaraiah,
LIG 100,
Dharma Reddy Colony,
K.P.H.B Colony
Kukatpally
Hyderabad - 500 072.

ORIGINAL 23 AUG 2002 621 MAS 2002


Signed) _____


Vijayavithal Thippannachar Mathad,
Flat No: 114, Adithya homes,
Adithya Nagar, opp. JNTU,
Pragathi Nagar Road,
Kukatpally,
Hyderabad-500 072.

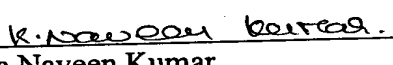
Signed) _____


Govindan Shanmugam
HIG-64, Bharat Nagar Colony
Hyderabad-500 018

Signed) _____


Maddipatla Madhavi,
B-393; LIG
Dr A S Rao Nagar
ECIL
Hyderabad-500 062.

Signed) _____


Kolla Naveen Kumar,
L.I.G, 957/1, flat No: 102,
Manoja buildings, III phase,
K.P.H.B Colony,
Hyderabad-500 072.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application
 - (a) complete specification (~~---13---~~ pages, in triplicate)
 - (b) abstract of the invention (~~---01---~~ page, in triplicate)
 - (c) drawings (~~---02---~~ pages, in triplicate)
 - (d) fee Rs. 5000.00 (five thousand rupees only) in A/C Payee Cheque vide No. "739066" dated August 12th drawn on HDFC Bank Limited, Lakdikapool, Hyderabad-500 004.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

**An Improved process for the preparation of crystalline
Form-II of Repaglinide**

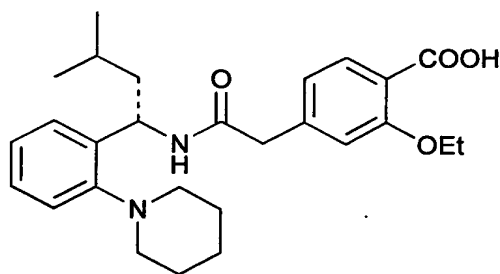
**Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.**

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

ORIGINAL
23 AUG 2004
621
15 SEP 2002

FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of crystalline Form-II of (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3-methyl-1-butyl)-amino carbonyl methyl] benzoic acid [(S)-Repaglinide], which is represented by the following Formula (1).



Formula (1)

BACK GROUND OF THE INVENTION:

Repaglinide is an anti diabetic drug and used as therapeutic agent for type-2 diabetic patients.

USP 5,216,167 specifically claims Repaglinide including its enantiomers and pharmaceutically acceptable salts. The patent describes the process for the preparation of Repaglinide, its enantiomers and related compounds in the experimental section.

The patent also discloses three crystalline polymorphic Forms for racemic Repaglinide, which are represented as Form-A, Form-B, and Form-C. The process for the preparation of these crystalline forms along with their interconversions is also described in the patent. The disclosed crystalline forms of Repaglinide are characterized by their IR spectra and visual melting point. The solvents involved in the crystallization process and their melting points are described as follows.

- **Form A:** Recrystallised from acetone / petroleum ether having a melting range of 90-92°C.
- **Form B:** Recrystallised from ethanol / water having a melting range of 140-142°C.
- **Form C:** Recrystallised from methanol having a melting range of 74-85°C.

The process for the preparation of (S)-enantiomer of Repaglinide is described in '167 patent, which comprises resolution of racemic 3-methyl-1- (2-piperidino-phenyl)-1-butyl amine with N-acetyl-L-glutamic acid to afford the (S)-enantiomer of corresponding amine. Thus, resulted amine is reacted with 3-ethoxy-4-ethoxy carbonyl-phenyl acetic acid to give ethyl ester of (S)-Repaglinide. The saponification of ester resulted (S)-Repaglinide and it is further recrystallised in petroleum ether / toluene, which is having a melting point of 102-104°C.

The '167 patent doesn't describes the XRD data of Form-A, Form-B and Form-C of racemic Repaglinide. The said patent has also not disclosed the crystalline structure of (S)-Repaglinide obtained in their process.

The inventors of the present invention have prepared the disclosed crystalline Form-A, Form-B and Form-C for racemic Repaglinide by following the process disclosed in USP '167 patent. These crystalline forms have been analyzed by XRD and the pattern of Form-A and Form-B for racemic Repaglinide is differing from each other. The polymorph Form-C is found to be an amorphous form, as the X-ray diffractogram has no well-resolved peaks.

The inventors of the present invention have also prepared the crystalline forms by following the process disclosed in the patent using S-Repaglinide. The crystalline forms obtained by recrystallizing the S-Repaglinide in solvent mixture acetone / pet. ether

(disclosed for preparation of Form-A of racemic Repaglinide) and ethanol/water

(disclosed for preparation of Form-B of racemic Repaglinide) are found to be same as per

their X-ray diffractograms. Hence, these crystalline forms for S-Repaglinide are

collectively designated as crystalline Form-I of S-Repaglinide for our convenience.

The 2-theta values and their relative intensity percentages of the above-obtained

crystalline forms of (S)-Repaglinide are furnished in the following Table-1.

Table-1:

Acetone/Pet. ether process		Ethanol/water process	
2-Theta	Intensity %	2-Theta	Intensity %
7.58	100	7.60	100
10.06	61.1	10.08	67.6
12.40	2.0	12.40	1.9
12.98	9.5	13.02	9.4
13.21	15.9	13.22	17.3
13.75	25.2	13.76	27.5
14.56	7.5	14.58	7.5
15.26	7.0	15.28	6.7
15.53	1.1	15.53	1.0
16.65	31.7	16.66	33.7
16.94	3.7	16.94	3.9
17.51	8.4	17.53	8.8
18.56	12.4	18.58	12.5
20.26	58.5	20.27	62.4
20.48	19.3	20.52	21.6
21.37	0.8	21.41	0.9
21.88	1.2	21.89	1.3
22.94	25.4	22.93	24.8
23.35	5.3	23.35	7.4
23.95	19.7	23.96	20.2
25.02	1.6	24.99	1.1
25.36	2.4	25.33	2.2
25.66	4.2	25.67	4.1
26.23	3.5	26.25	3.8
26.65	8.4	26.65	9.3
27.75	7.9	27.76	8.4

28.73	0.9	28.73	1.1
29.47	1.1	29.46	1.7
29.77	2.8	29.77	2.9
30.86	15.3	30.88	16.7
31.61	1.3	31.56	1.0
32.49	0.8	32.49	0.9
35.46	1.4	35.46	1.1
36.09	0.9	36.07	1.1
37.02	1.8	37.04	1.9
38.84	1.8	38.89	2.4
39.48	1.1	39.49	1.0
43.55	1.1	43.52	1.0
44.08	1.1	44.09	0.9

The compound obtained by recrystallizing the S-Repaglinide in neat methanol (disclosed for preparation of Form-C of racemic Repaglinide) is resulted an amorphous form, since its X-ray diffractogram has no well-resolved peaks.

Apart from these Polymorphic study, the inventors of the present invention have also prepared the S-Repaglinide by following the process disclosed in USP '167 (example 106) and analyzed the crystalline structure by X-ray diffractogram, which differs with the above designated crystalline Form-I of (S)-Repaglinide. Hence, the resulted crystalline form, which involves the recrystallisation of S-Repaglinide from toluene/petroleum ether, is designated as crystalline Form-II of (S)-Repaglinide for our convenience.

The 2-theta values and their relative intensity percentages of the above-designated crystalline Form-II of (S)-Repaglinide are furnished in Table-2.

No other relevant references have described the crystalline structure of either racemic or enantiomers of Repaglinide.

The process disclosed in the USP '167 for the preparation of Form-II of (S)-Repaglinide is having some disadvantages as it involves the usage of mixture of solvents. The said solvents may not be separated after recovery. The process also involves high volume of

solvents to isolate the Form-II of (S)-Repaglinide. The yield obtained in this process is much low; hence, the process is not suitable for scale up.

The aspect of the present invention relates to provide an improved process for the preparation of above designated crystalline Form-II of (S)-Repaglinide by overcoming the disadvantages of prior art process. The process of the present invention involves a single solvent, which can be easily recoverable with a minimum loss.

The process for the preparation of crystalline Form-II of present invention is cost effective since the solvent is recoverable and yield of the compound is much higher than the prior art process. The crystalline Form-II obtained in the present invention is having high purity i.e. >99.0%.

The novel crystalline Form-II of (S)-Repaglinide obtained in the present invention is characterized by its X-ray diffractogram and IR spectra.

The novel crystalline Form-II of the present invention is free flowing and non-solvated crystalline solid and hence may be useful in the preparation of pharmaceutical formulations.

The process of the present invention is simple, non-hazardous and commercially viable.

SUMMARY OF THE INVENTION:

The present invention relates to provide an improved process for the preparation of crystalline Form-II of (S)-Repaglinide.

An improved process for the preparation of crystalline Form-II of (S)-Repaglinide comprises the recrystallisation of crystalline or amorphous form of (S)-Repaglinide in toluene.

The present invention also relates the preparation of crystalline Form-II of (S)-Repaglinide from crystalline Form-I or Form-III or an amorphous form of (S)-Repaglinide.

The processes of the present invention are simple, non-hazardous and commercially viable.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWING:

Fig. 1 is characteristic X-ray powder diffractogram of crystalline Form-II of (S)-Repaglinide obtained as per process disclosed in USP '167 (Example-106).

Fig.2 is characteristic X-ray powder diffractogram of crystalline Form-II of (S)-Repaglinide obtained in the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to provide an improved process for the preparation of crystalline Form-II of (S)-Repaglinide.

The crystalline Form-II of (S)-Repaglinide is characterized by X-ray diffractogram, Infrared spectra and visual melting point.

The X-ray diffractogram of crystalline Form-II of (S)-Repaglinide of the present invention is measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The X-ray diffractogram of crystalline Form-II of (S)-Repaglinide obtained by the process disclosed in the USP '167 is substantially as depicted in Figure (1).

The X-ray diffractogram of crystalline Form-II of (S)-Repaglinide obtained in the present process is substantially as depicted in Figure (2).

The characteristic peaks (in 2-theta values) and their relative intensities (in percentage) of crystalline Form-II of present invention along with prior art crystalline Form-II of (S)-Repaglinide are shown in the following table (2).

Table-2:

Crystalline Form-II obtained as per the process disclosed in USP '167		Crystalline Form-II obtained as per the present process	
2-Theta	Intensity %	2-Theta	Intensity %
7.586	100	7.57	100
5.415	83.3	5.383	60.6
19.566	44.2	19.527	40.3
16.352	38.2	16.311	25
22.939	29.5	22.904	21.4
25.938	15.3	20.979	11.1
21.044	14.5	25.871	10.5
10.564	13.1	10.551	10
14.039	12	14.007	10
18.812	10.9	18.775	8.6
11.025	9	10.966	6.8
27.558	5.3	12.066	3.7
23.698	4.6	27.524	3.7
12.102	4.3	23.65	3.2
20.267	4.2	9.081	2.8
9.104	3.7	20.18	2.5
17.05	2.8	15.222	2.3
15.324	2.5	17.174	2
12.701	2.3	14.461	1.6
9.696	1.5	12.689	1.4
29.052	1.5	34.979	1.3
30.107	1.4	29.08	1
31.22	1.1	31.165	1
33.113	1.1	33.074	1
-----	-----	9.648	0.9
-----	-----	30.088	0.8
-----	-----	31.934	0.4

The crystalline Form-II of (S)-Repaglinide obtained in the present invention is also characterized by Differential Scanning Colorimetry thermogram, which was analyzed on

Schimidzu differential scanning colorimeter in a temperature range of 25-160°C with a heating rate of 5°C/minute under Nitrogen with a flow rate of 50.0 ml/minute.

The Differential Scanning Colorimetry thermogram of crystalline Form-II of (S)-Repaglinide exhibits a significant endo-endo pattern with peaks around 105°C and 132°C.

Accordingly, an improved process for the preparation of crystalline Form-II of (S)-Repaglinide, which comprises;

- a) dissolving crystalline or an amorphous form of (S)-Repaglinide in aromatic hydrocarbon solvents comprising of benzene, toluene, ethyl benzene or xylene, preferably toluene at a temperature of 50-100 °C, preferably at 70-75 °C;
- b) cooling the reaction solution of step (a);
- c) stirring the reaction solution of step (b) till the solid substantially separates;
- d) filtering the separated solid obtained in step (c) by conventional methods;
- e) drying the resulting solid of step (d) under vacuum at a temperature of 30 to 90°C to a constant weight to afford the crystalline Form-II of (S)- Repaglinide.

The crystalline Form-II of S-Repaglinide obtained in the above process is having >99.0% purity. The resulted crystalline Form-II of (S)-Repaglinide of the present invention is characterized by X-ray diffractogram and is substantially identical with the crystalline compound obtained by the process disclosed in the USP '167. Hence, it infers the crystalline structure of these two compounds is similar.

The process of the present invention to prepare crystalline Form-II of (S)-Repaglinide is advantageous over the prior art process as it involves a single solvent toluene for recrystallisation to afford the desired crystalline form.

The process of the present invention is simple, eco-friendly and industrially scalable.

Thus, the present invention offers an improved process for the preparation of crystalline Form-II of (S)-Repaglinide.

It is noteworthy to mention that the process for the preparation of crude (S)-Repaglinide is followed as disclosed in USP '167 patent. The crystallization procedure for the preparation of Form-I and Form-II of (S)-Repaglinide is also disclosed in the same patent.

The process for the preparation of crystalline Form-III and an amorphous form of (S)-Repaglinide is disclosed in our co-pending Indian patent applications.

The present invention is described in detail with examples given below that are provided by the way of illustration only and therefore, should not be construed to limit the scope of invention.

EXAMPLE-1:

Dissolved the crude (S)-Repaglinide (100.0 grams) in toluene (2.0 liters) and heated to a temperature of 70-75°C till clear solution results. Then the reaction solution was cooled to a temperature of 10-15°C and stirred till the solid separates. Then the separated solid was filtered, washed with toluene (200.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired crystalline Form-II of (S)-Repaglinide.

(Weight: 77.4 grams, Visual Melting Point: 101-104°C, M.C. by KF: 0.18%).

EXAMPLE-2:

Dissolved the crystalline Form-I of (S)-Repaglinide (5.0 grams) in toluene (100.0 ml) and heated to a temperature of 60-65°C till clear solution results. Then the reaction solution was cooled to a temperature of 10-15°C and stirred till the solid separates. The separated

solid was filtered, washed with toluene (10.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired crystalline Form-II of (S)-Repaglinide.

(Weight: 4.4 grams, M.C. by KF: 0.16%).

EXAMPLE-3:

Dissolved the crystalline Form-III of (S)-Repaglinide (20.0 grams) in toluene (400.0 ml) and heated to a temperature of 60-65°C till clear solution results. Then the reaction solution was cooled to a temperature of 10-15°C and stirred till the solid separates. The separated solid was filtered, washed with toluene (40.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired crystalline Form-II of (S)-Repaglinide.

(Weight: 18.2 grams, M.C. by KF: 0.15%).

EXAMPLE-4:

Dissolved the amorphous form of (S)-Repaglinide (10.0 grams) in toluene (200.0 ml) and heated to a temperature of 60-65°C till clear solution results. Then the reaction solution was cooled to a temperature of 10-15°C and stirred till the solid separates. The separated solid was filtered, washed with toluene (10.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired crystalline Form-II of (S)-Repaglinide.

(Weight: 9.4 grams, M.C. by KF: 0.06%).

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWINGS:

Fig-1 is characteristic X-ray powder diffraction pattern of crystalline Form-II of (S)-Repaglinide [Prepared as per the process disclosed in USP '167 (Example-106)].

Vertical axis: Intensity (CPS); Horizontal axis; Two Theta (degrees).

The significant 2-theta values are 5.145, 7.586, 9.104, 9.696, 10.564, 11.025, 12.102, 12.701, 14.039, 15.324, 16.352, 17.05, 18.812, 19.566, 20.267, 21.044, 22.939, 23.698, 25.938, 27.558, 29.052, 30.107, 31.22 and, 33.113 degrees two-theta.

Fig-2 is characteristic X-ray powder diffraction pattern of crystalline Form-II of (S)-Repaglinide obtained in the present invention.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

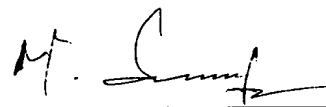
The significant 2-theta values are 5.383, 7.57, 9.081, 9.648, 10.551, 10.966, 12.066, 12.689, 14.007, 14.461, 15.222, 16.311, 17.174, 18.775, 19.527, 20.18, 20.979, 22.904, 23.65, 25.871, 27.524, 29.08, 30.088, 31.165, 31.934, 33.074 and 34.979 degrees two-theta.

We claim:

1. An improved process for the preparation of crystalline Form-II of (S)-2-Ethoxy-4-[N- (1-(2-piperidino-phenyl)-3-Methyl-1-butyl)-amino carbonyl methyl] benzoic acid [(S)-Repaglinide)] comprises of
 - a. dissolving crystalline or amorphous form of (S)-Repaglinide in aromatic hydrocarbon solvents comprising of benzene, toluene, ethyl benzene or xylene, preferably toluene at a temperature of 50-100 °C, preferably at 70-75 °C;
 - b. cooling the reaction solution of step (a);
 - c. stirring the reaction solution of step (b) till the solid separates;
 - d. filtering the separated solid obtained in step (c) by conventional methods;
 - e. drying the resulting solid of step (d) under vacuum at a temperature of 30-90 °C to a constant weight to afford the crystalline Form-II of (S)-Repaglinide.
2. The process according to claim 1 of step (a), where in the aromatic hydrocarbon solvent is toluene.
3. The crystalline compound according to claim 1 of step (a) is Form-I of (S)-Repaglinide.
4. The crystalline compound according to claim 1 of step (a) is Form-III of (S)-Repaglinide.
5. The improved processes for the preparation of crystalline Form-II of (S)-Repaglinide is substantially as herein described and exemplified.

Dated 22nd August, 2002

Signed)



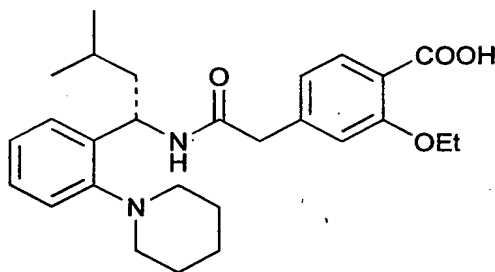
Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

ABSTRACT

Title of the Invention: An improved process for the preparation of crystalline Form-II of (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3-methyl-1-butyl)-amino carbonyl methyl] benzoic acid [(S)-Repaglinide]

The present invention relates to an improved process for the preparation of crystalline Form-II of (S)-Repaglinide of Formula (1). The process for the preparation of crystalline Form-II of (S)-Repaglinide comprises the recrystallisation of crystalline or an amorphous form of (S)-Repaglinide in aromatic solvents such as toluene.

The process of the present invention is simple, non-hazardous and commercially viable over prior art process.



Formula (1)

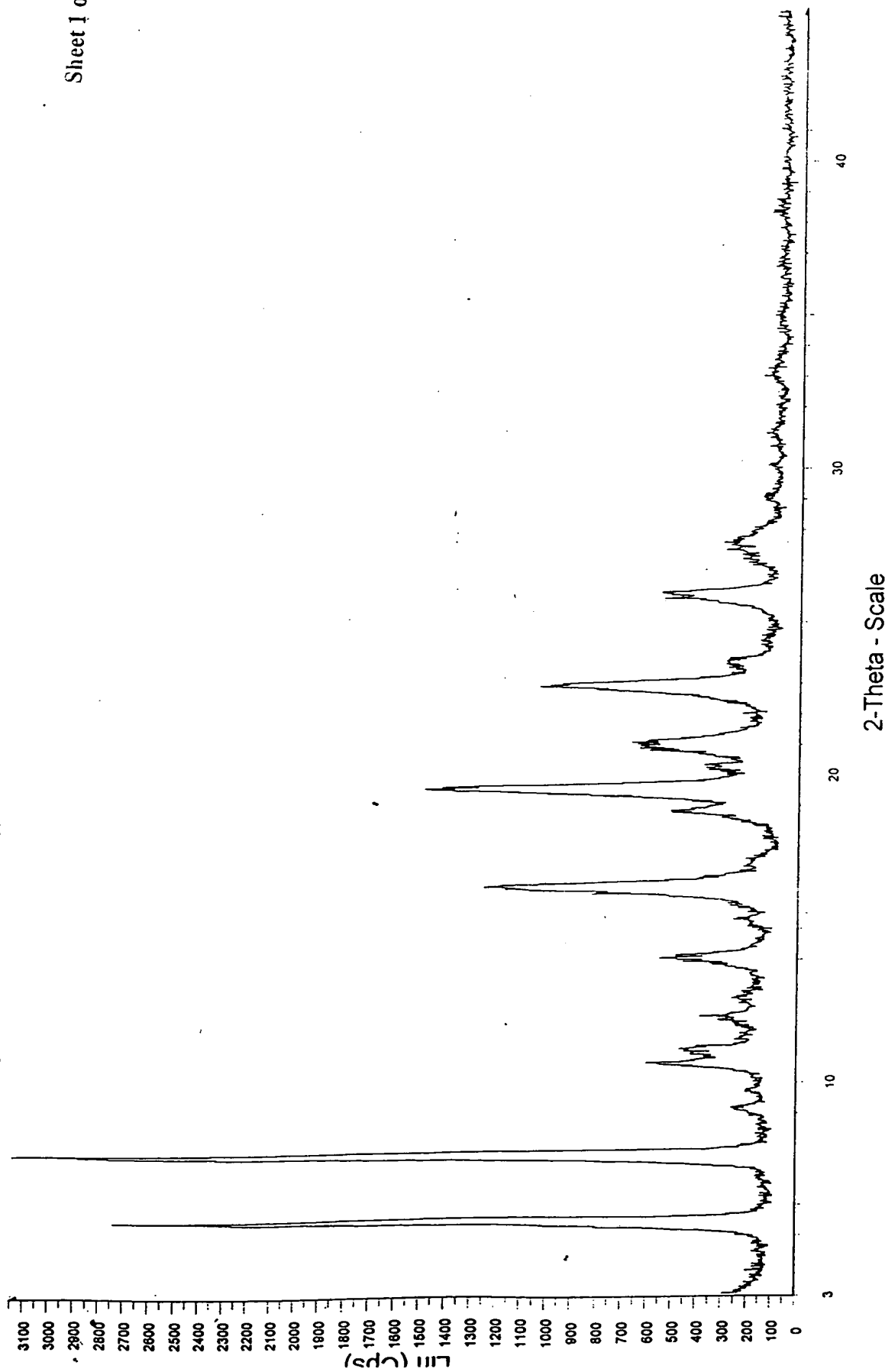


Fig. 1

M. Sanyal

MANNE SATYANARAYANA REDDY

ORIGINAL. 43 AUG 2009

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Fig. 1

15-8-2009

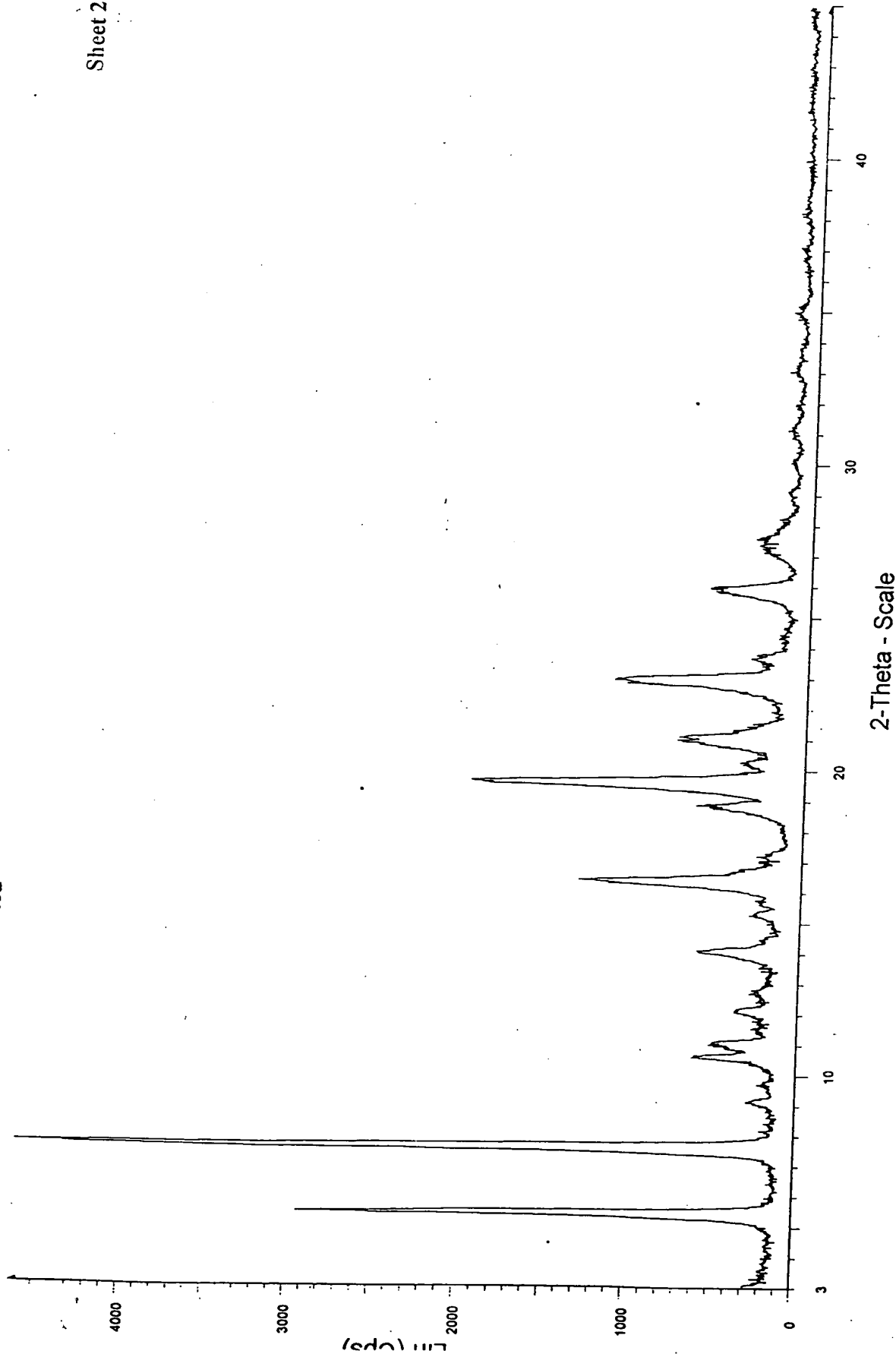


Fig.2

2000 1500 1000 500

M. Sanyal

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16.9.2007
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